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## Plasma Renin Activity and Aldosterone: Correlations with Moderate Hypohydration

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Adult male test subjects ( $n = 16$ ) were assigned to one of three clothing configurations (Army fatigues, fatigues with impermeable chemical protective garments, and fatigues with protective garments plus protective masks) prior to exercise (level treadmill, 1.11 m/s, 50 min/h, 6 h) in a moderate (wet bulb globe temperature, WBGT = 23°C) environment with ad lib water consumption. When protective masks were worn, two through-mask drinking systems were evaluated: the current gravity-fed system for fluid delivery and a new system utilizing a small hydraulic pump (Fist-Flex). Antecubital blood samples were taken prior to the start of and subsequent to the completion of exercise and analyzed for fluid-electrolyte regulatory hormones. During all trials with chemical protective garments, plasma renin activity (PRA) and aldosterone levels (PA) were significantly ( $p < 0.05$ ) elevated following the exercise protocol while neither was affected during exercise in fatigues only. Individual hypohydration levels during all trials ranged from low (0.84%) to moderate (4.04%). Levels of PRA were closely correlated ( $r = 0.635$ ,  $t = 4.35$ ,  $p < 0.001$ ) with hypohydration as measured by percentage of body weight lost during the 6 h trial. Likewise, PA was also correlated ( $r = 0.47$ ,  $t = 2.81$ ,  $p < 0.01$ ) with body weight loss. We concluded from this study that PRA and PA responses were exacerbated in moderate environments by the additional heat stress, sweat rate, and dehydration caused by the impermeable garments. Further, the logistical difficulty inherent in delivering fluid through the chemical protective mask reduced voluntary consumption, increased hypohydration, and elicited the greatest elevations in PRA and PA. Finally, even at these modest levels of hypohydration, the intensity of the PRA and PA responses were correlated with hypohydration level.

IN HIS RECENT book Rowell (30) notes three generalized mechanisms by which the biosynthesis of renin may be stimulated: increased renal sympathetic activity which is sensitive to  $\beta$ -blocking agents, a decrease in the pressure stretching afferent arterioles of the glom-

erulus, and a reduction in the sodium levels perceived by cells of the distal tubules. The increase in plasma renin activity (PRA), if it persists for hours or days, can stimulate the synthesis and release of aldosterone by the adrenals; aldosterone, in turn, promotes the reabsorption of sodium by the distal tubules of the kidney and thus the retention of water by the vasculature. Thus, PRA and circulating aldosterone, in conjunction with vasopressin (antidiuretic hormone), are the humoral factors most instrumental in the regulation of fluids and electrolytes in mammalian systems.

It is thus not surprising that there is available an extensive literature on the effects of sedentary heat exposure and exercise in the heat and accompanying hypohydration on plasma levels of aldosterone (PA) as well as PRA. Kosunen *et al.* (26) and Adlerkreutz *et al.* (1) reported that just 20 min after sedentary exposure to the intense heat of a sauna (85–90°C), levels of both PA and PRA were significantly elevated even in experienced sauna users. Similarly, Dumoulin *et al.* (9) exposed test subjects to an 80°C ambient temperature for 20 min and observed increments in both PRA and PA. Even under more moderate environmental conditions, it has been well established that sedentary exposure to hot ambient conditions is accompanied by hormonal adaptations to reduce fluid and electrolyte loss; both PRA (11,12) and PA (12,14) play pivotal roles in these responses.

When physical exercise is superimposed upon the stress of a hot environment, then the endocrinological responses designed to protect and sustain fluid and electrolyte levels are exacerbated. Finberg *et al.* (13) reported that increments in PRA following exercise at 50°C could be lessened when the experiment was executed during the summer in comparison to the winter. When we dehydrated subjects by 5% of body weight, significant elevations were observed in PA and PRA even before exercise in the heat, and these increments persisted during a heat/exercise trial (16). More recently, we dehydrated test subjects by 3, 5, and 7% of original body weight, and reported that increasing the intensity of hypohydration from 3% to 5% was accom-

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panied by increased PRA and PA during exercise in the heat (18). Interestingly, between 5% and 7% hypohydration, wherein no further absolute decrements in plasma volume were reported (31), we also observed no additional elevation in either PRA or PA (18). In these earlier studies drinking was permitted at the completion of each exercise interval only to the extent necessary to rehydrate each subject to the appropriate pre-exercise body weight.

In the current studies we had the opportunity to assess the endocrinological responses of test subjects who underwent moderate intensities of "voluntary dehydration" (22,24): in this case, the voluntary dehydration was the direct result of inconvenience in fluid ingestion since adequate supplies of water were conveniently available, and subjects were instructed to drink as much as they wished. Test subjects were configured in impermeable chemical/biological protective garments, and in one experimental scenario were required to ingest fluids through a protective mask, a situation which ordinarily reduces fluid ingestion contributing to dehydration. These experimental contingencies elicited various levels of hypohydration ranging between 0.84% and 4.04% of initial body weight. The numbers of test subjects and experimental trials allowed us to examine the correlation between endocrinological responses and these moderate levels of hypohydration (% body weight loss); such correlations had not been previously reported.

## MATERIALS AND METHODS

Sixteen young adult male test subjects were recruited and thoroughly briefed on the nature and purpose of the current study; each signed an agreement of informed consent, and retained the right to withdraw at any time without retribution. Subjects were not heat-acclimated and were judged healthy by a physical examination. At 0645 hours of each experimental day, subjects (Ss) reported to the climatic chamber facility for a light breakfast consisting of 450 ml of instant breakfast beverage, toast, butter, jam, and 450 ml of orange juice. Urinary specific gravity (S.G., refractometry) was tested postprandially to assure adequate hydration (S.G. < 1.03).

Immediately following this breakfast, a nude body weight was obtained and used to calculate percent body weight loss and sweat rates. Then Ss were instrumented (three point electrocardiographic monitoring, rectal temperature, and skin temperature of the forearm, calf, and chest) for both data collection and to assure safety criteria. The rectal thermistor was inserted to a depth of 10 cm beyond the anal sphincter. Each test subject performed 2 trials, and the clothing and drinking configurations were randomized. Following instrumentation test subjects were assigned to one of four clothing and masked configurations on each experimental day: standard army fatigues ( $n = 7$ ; fatigues plus chemical protective garments ( $n = 7$ ); fatigues with chemical protective garments and protective masks using the current gravity-fed system for fluid delivery ( $n = 8$ ); and fatigues with chemical protective garments and protective masks using a hydraulic pump for fluid delivery through the mask ( $n = 8$ ). All Ss wore socks and sneakers dur-

ing all experimental trials. These experimental configurations assured variable levels of thermal stress, sweat rates, and difficulty in drinking since masked drinking required a tube which led from a canteen and connected to a mouthpiece of the mask. Using the current system for masked drinking, Ss may raise the canteen above the level of the mask inlet and allow the fluid to flow by gravity and suction (current system, CS); a system under development (FIST-FLEX™, FF, Wesleyan Co., Chicago, IL) provides a small hand-compression device near the collapsible canteen to serve as a hydraulic pump to deliver fluids through the mask. After test subjects were instrumented and appropriately garmented, careful assessment of clothed-instrumented body weight was made (Sauter balance,  $\pm 50$  g accuracy).

Ss then entered a large environmental chamber which was maintained at moderate environmental conditions:  $T_{db} = 31^\circ\text{C}$ ,  $T_{wb} = 19^\circ\text{C}$ , relative humidity = 30%, and windspeed = 1.2 m/s. These ambient conditions produced a wet bulb globe temperature (WBGT) of approximately  $23^\circ\text{C}$ . Upon entry into the chamber, Ss were instructed to remain standing quietly for at least 20 min as an equilibration period for body fluids and fluid compartments (23); further, this equilibration was also necessary since the second blood sample was taken upon completion of exercise, and body posture affects the dependent variables of interest. Following this interval, a small sample of blood was obtained by venepuncture from a superficial (antecubital) arm vein.

This was immediately followed by a 6h interval of 50 min walk, 10 min rest with uninterrupted monitoring of core temperature, skin temperature, and heart rate. Criteria for cessation of the test included a core temperature  $>39.5^\circ\text{C}$  or heart rate  $>180$  bpm. Subjects walked on large treadmills (4 man) set at a flat grade and at a rate of 1.11 m/s. Thus, if the entire test protocol were completed in a particular configuration, then Ss walked a total of 20 km. Water ( $31^\circ\text{C}$ ) was constantly available at arm's length from each volunteer; field water supplies were duplicated by adding 16 mg iodine/liter before distribution to canteens. Ss were encouraged to drink *ad lib*, but information on hydration status (assessed during each rest period by weighing) was not provided. During each 10-min rest period, Ss sat quietly at their respective work station while physiological monitoring continued.

Immediately upon completion of the final walk, or when a volunteer requested removal from the study, and without further drinking, Ss remained standing for acquisition of a final blood sample. Blood samples were processed immediately. Hematocrit was immediately determined in triplicate by microcentrifugation while hemoglobin was quantitated using the cyanmethemoglobin method. Changes in plasma volume were calculated using the equations of Dill and Costill (8). Ethylenediaminetetraacetate (EDTA)-treated whole blood was centrifuged ( $4^\circ\text{C}$ , 10000 g), and aliquots of plasma were frozen ( $-20^\circ\text{C}$ ) and stored for subsequent analysis. Angiotensin I levels were estimated from quantitation of plasma renin activity using radioimmunoassay test kits purchased from New England Nuclear Corp. (Billerica, MA) according to procedures noted in their technical

bulletin (Angiotensin I ( $^{125}$ I) Radioimmunoassay Kit-Instruction Manual). When angiotensin converting enzyme and angiotensinases are appropriately inhibited, it has been demonstrated that the accumulation of angiotensin I accurately reflects PRA. PRA was optimally assessed at a pH of 6.0 at 37°C during a 1-h incubation period. Ordinarily, control levels for healthy, normotensive upright men range from 1.0 to 4.0 ng angiotensin I formed per hour per milliliter plasma by this method (15). Plasma aldosterone levels (PA) were measured using radioimmunoassay test kits obtained from Diagnostics Products Corp. (Los Angeles, CA); procedures followed are described in their technical bulletin (Coat-A-Count<sup>®</sup>-No Extraction Aldosterone). These analyses ordinarily provide values ranging from 5–30 ng/dl for normotensive adult men. Plasma cortisol (PC) levels were estimated using radioimmunoassay test kits purchased from New England Nuclear Corp. (Billerica, MA) after procedures outlined in the technical bulletin (Cortisol ( $^{125}$ I) Radioimmunoassay Kit-Instruction Manual). Using these methods PC levels are generally reported to range from 5–25 ug/dl, with the variability dependent largely upon the time of day at which the blood samples are taken (27).

The effects of exercise in the warm environment were statistically analyzed by the paired *t*-test for dependent data (28). Correlation coefficients were determined by linear regression analysis, and the null hypothesis was rejected at  $p < 0.05$ .

## RESULTS

When dressed in standard Army fatigues, all Ss completed the 6 exercise intervals, and with the chemical/biological protective uniform over the standard Army fatigues, 6 of 7 Ss completed the 20 km. However, when the chemical/biological protective uniform was worn in combination with the masked configuration, only 5 of 16 trials were completed. In these cases blood was taken in the upright posture at termination of the trial.

Fig. 1 demonstrates the effects of clothing and masked configurations and exercise on circulating cortisol levels. PC was monitored in this experiment as a metric of generalized adrenocorticotrophic activity or stress level (17,20) induced by the combination of exercise, warm environment, and, in certain cases, encapsulation. The results indicate that for three of the experimental scenarios (fatigues, protective uniform, and protective uniform with mask, current system) there were no increases in PC levels. During a single experimental trial (protective uniform plus mask, Fist-Flex) there did occur a significant ( $p < 0.01$ ) elevation in mean post- vs. pre-exercise cortisol level (22.1 ug/dl, vs. 13.5 ug/dl, respectively). The mean post-exercise value was somewhat skewed by a value of 44 ug/dl for a single test subject; interestingly, this particular individual also displayed one of the highest percentage body weight losses (3.8%) as well as elevations in PRA (18.8 ng  $\cdot$  ml<sup>-1</sup>  $\cdot$  h<sup>-1</sup>) and PA (76.2 ng/dl) subsequent to exercise while encapsulated; the consistent pattern of hormonal elevations in this test subject probably indicates a true adrenocorticotrophic response to moderate dehydration.

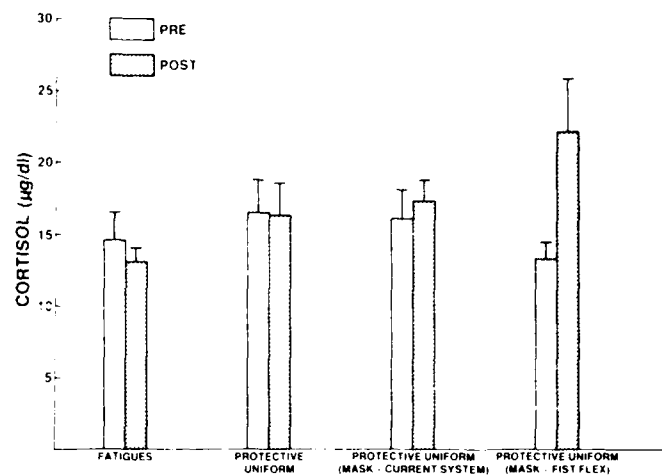


Fig. 1. The effects of the various clothing and accessory configurations on plasma cortisol prior and subsequent to exercise (1.11 m/s) in a moderate (23°C, WBGT) environment. Mean values  $\pm$  S.E.M. are depicted for each group: fatigues,  $n = 7$ ; protective uniform,  $n = 7$ ; protective uniform, mask-current system,  $n = 8$ ; protective uniform, mask-fist-flex,  $n = 8$ . Each test subject performed two trials and the clothing configuration was randomized.

Fig. 2 illustrates mean levels of PRA prior and subsequent to exercise in the various experimental configurations. The results clearly indicate that when clothed in standard Army fatigues and with *ad lib* drinking water available within reach, Ss completed the 6 h interval of 50/10 min work/rest cycles under these conditions with no effect on PRA. However, when the impermeable protective uniform and the protective uniform with the mask were added to the clothing configuration, the heat stress was increased, and PRA was elevated significantly ( $p < 0.025$ ) in all three trials. It is interesting to observe that in the "fatigue trial" Ss lost 1.94% (1.43 kg) of their initial body weight while in the "fatigue plus protective uniform trial," the mean weight loss was 2.16% (1.52 kg) ( $p = ns$ ). Moreover, when PRA levels

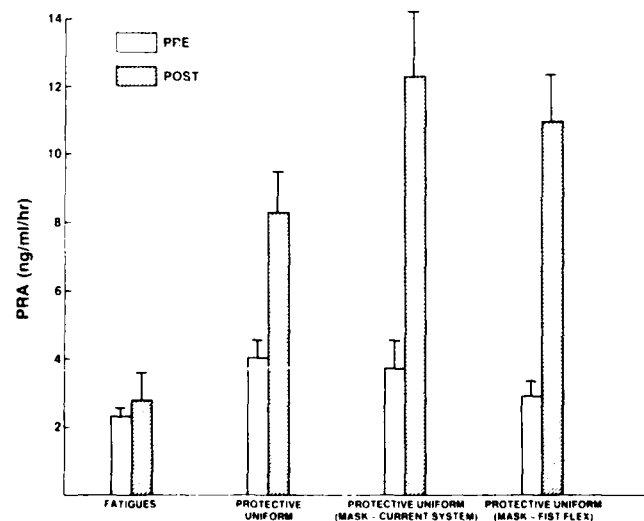


Fig. 2. The effects of the various experimental configurations and exercise in a moderate environment on plasma renin activity. All conditions are as explained under Fig. 1.

following exercise were correlated with individual weight losses (Fig. 3), the data manifested a highly significant ( $p < 0.001$ ) correlation. Depicted in this figure is the line of best fit for these data. Further, in the encapsulated and masked configurations, mean body weight losses were highest (2.56%, 1.84 kg and 2.81%, 2.06 kg) as were mean PRA ( $12.3 \text{ ng} \cdot \text{ml}^{-1} \cdot \text{h}^{-1}$  and  $11.0 \text{ ng} \cdot \text{ml}^{-1} \cdot \text{h}^{-1}$ ).

Because of the correlation of PRA and percentage decrement in body weight we also examined the association between post-exercise PRA and rate of body weight loss (g/min), percentage change in plasma volume, and final (approximately maximal) heart rate. PRA was positively correlated with rate of weight (water) loss ( $r = 0.47$ ,  $t = 2.82$ ,  $p < 0.01$ ) and inversely with calculated decrement in plasma volume ( $r = 0.51$ ,  $t = 3.15$ ,  $p < 0.005$ ). The data for final heart rate and PRA were depicted in Fig. 4 and demonstrate a close correlation between PRA and final heart rate ( $r = 0.681$ ,  $t = 4.83$ ,  $p < 0.001$ ).

Fig. 5 illustrates generally analogous results for the effects of the experimental configurations and exercise on PA. Thus, following the "fatigue trial," PA levels are not significantly different from those recorded prior to the experimental interval. However, in each of the three remaining configurations, post-exercise blood samples manifested significantly ( $p < 0.05$ ) increased levels of PA. Fig. 6 demonstrates that individual levels of PA are less closely correlated with percent body weight loss ( $p < 0.01$ ) than PRA ( $p < 0.001$ , Fig. 3). Again, the line of best fit is shown for these data.

## DISCUSSION

Even at these relatively low levels of hypohydration (range = 0.84% – 4.04%), our data show a strong correlation between PRA and PA responses to exercise in the various clothing configurations. Although there have been a considerable number of reports documenting the analogous responses of circulating levels of PRA and PA to sedentary heat exposure (3,14) and exercise in the heat (4,7), we have reported that the acquisition of heat acclimation has a greater moderating influence on PRA than PA responses (16). In a later experiment we reported (18) that hypohydration apparently had more notable effects on PRA than PA during exercise in

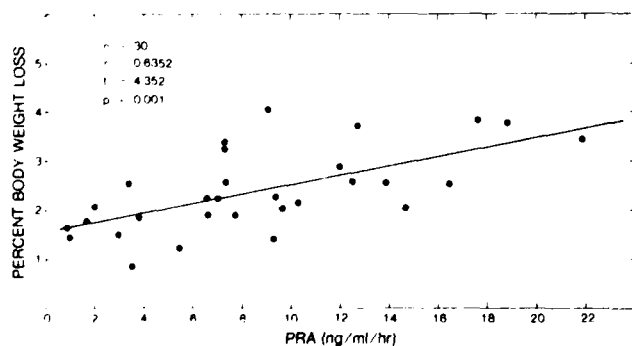


Fig. 3. Scatter plot and the line of identity of individual values of percentage of body weight loss during the exercise scenario and levels of plasma renin activity. The correlation coefficient was calculated by least squares regression analysis. Data for all subjects and trials are depicted.

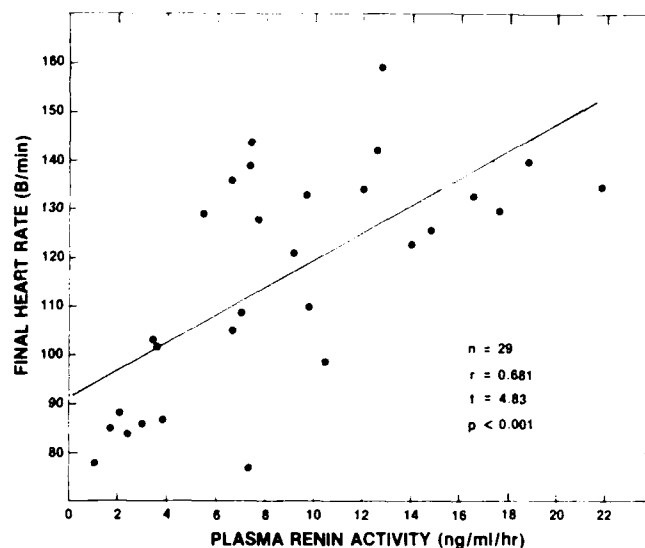


Fig. 4. Scatter plot and the line of identity of individual values of final heart rate (approximate maximal heart rate) and levels of plasma renin activity. All conditions and parameters are as depicted under Fig. 3.

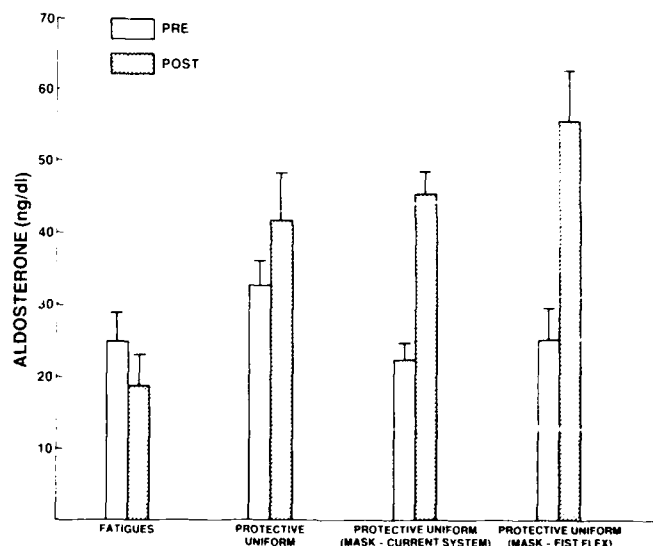


Fig. 5. The effects of the various experimental configurations and exercise in a moderate environment on levels of plasma aldosterone. All conditions are as explained under Fig. 1.

the heat. These earlier results are compatible with those of the current study wherein elevations in PRA were more closely correlated ( $r = 0.635$ ) with hypohydration as measured by percentage of initial body weight loss than were increments in PA ( $r = 0.469$ ). While the responses of both PRA and PA to heat exposure and exercise in the heat are generally similar, Brandenberger *et al.* (5) used propranolol to increase PA responsiveness to heat exposure while the PRA response was significantly decreased by propranolol administration. Likewise, Konikoff *et al.* (25) used salt loading to dissociate the effects of exercise in a hot, dry climate on PA and PRA responses. They reported (25) that whereas salt supplementation decreased PA during work in the heat, salt intake had no effect on PRA responses. Clearly, while plasma renin has been documented to partially control aldosterone secretion and

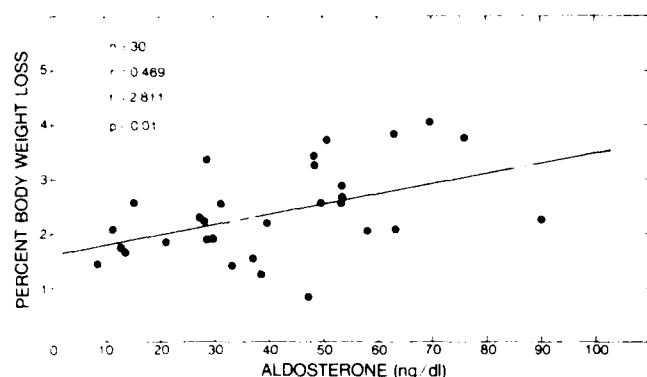


Fig. 6. Scatter plot of the correlation between percentage of body weight loss during the exercise scenario and aldosterone levels. All parameters are as indicated under Fig. 3.

release, experimental manipulation can dissociate these responses.

The work of Brandenberger *et al.* (4) indicated that whereas increments in PRA during exercise in the heat could be prevented by adequate water consumption, ingestion of isotonic fluid containing electrolytes and sucrose was necessary to offset completely increments in PA. Alternatively, Francis and MacGregor (19) reported that consumption of an electrolyte-rich fluid during exercise in the heat was equally effective in attenuating increments in both PA and PRA. Geysant *et al.* (21) assessed hormonal levels after a prolonged training period, and observed that while PA was unaffected, resting levels of PRA were reduced; they attributed this response to the increased plasma volume subsequent to training. Thus, these are further indications that the responses of PRA to heat exposure/exercise may be more sensitive to the hydrational status of the test subjects while PA control may be affected more prominently by electrolyte status.

The design of the current study was ideal to elicit moderate, but variable, levels of hypohydration even at the mild WBGT (23°C) selected. Ordinarily, fluid intake during a march in a real or simulated tropic or desert environment is a function not only of work rate, clothing, and environmental conditions, but also of the temperature and palatability of the fluids available (24), time available for rehydration (29), accessibility and convenience of fluids (10) and a variety of factors such as thirst, gastric distention, and hot weather experience which may vary significantly among test subjects. While several of these variables were consistent among test subjects and test scenarios, the necessity to consume water through a tube/mouthpiece configuration in the masked ensemble assured variable levels of moderate hypohydration. Further, it is well-recognized that when individuals work acutely in warm or hot environments, fluid replacement will ordinarily not compensate for fluid losses in sweat and urine during the course of the exercise (2,6,22). This combination of factors provided the ideal range of graded hypohydration levels required to evaluate the association between PRA/PA and these levels.

We have concluded from these results that responses of fluid- and electrolyte-regulatory hormones to exercise even in a relatively moderate environment may be

enhanced by protective garments which clearly exaggerate the level of heat stress. Further, decreasing the facility and convenience of rehydration by adding a through-mask/tube contingency for fluid consumption contributed to increased hypohydration, and hormonal levels were consistently highest during these trials. Even at the relatively moderate hypohydration levels elicited by these conditions, individual PRA and PA responses were significantly correlated to percent body weight loss. Additionally, post-exercise PRA was positively correlated with the rate of weight (water) loss and inversely correlated with calculated changes in plasma volume, but were most closely correlated with final (maximal) heart rates. These data indicate that the intensity of endocrinological responses adaptive to fluid and electrolyte conservation are extremely sensitive to the level of hypohydration, and hence physiological cost, of the heat/exercise stress.

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